PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
RONALD I. EISENSTEIN
NIXON PEABODY LLP
100 SUMMER STREET
BOSTON, MA 02110

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing (*day/month/year*)	23 AUG 2005
Applicant's or agent's file reference 700953-53671-PCT	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date (*day/month/year*)	Priority date (*day/month/year*)
PCT/US04/38643	12 November 2004 (12.11.2004)	12 November 2003 (12.11.2003)

International Patent Classification (IPC) or both national classification and IPC

IPC(7): C07H 21/02; C12N 15/00; A61K 48/00 and US Cl.: 536/23.1; 435 320.1; 514, 44

Applicant

THERION BIOLOGICS CORPORATION

1. This opinion contains indications relating to the following items:

- [X] Box No. I — Basis of the opinion
- [ ] Box No. II — Priority
- [ ] Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- [ ] Box No. IV — Lack of unity of invention
- [X] Box No. V — Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- [ ] Box No. VI — Certain documents cited
- [ ] Box No. VII — Certain defects in the international application
- [ ] Box No. VIII — Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(*b*) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Ram Shukla

Form PCT/ISA/237 (cover sheet) (January 2004)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US04/38643

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material

      ☐ in written format

      ☐ in computer readable form

   c. time of filing/furnishing

      ☐ contained in international application as filed.

      ☐ filed together with the international application in computer readable form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US04/38643

Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 1-24	YES
	Claims NONE	NO
Inventive step (IS)	Claims None	YES
	Claims 1-24	NO
Industrial applicability (IA)	Claims 1-24	YES
	Claims NONE	NO

2. Citations and explanations:

Claims 1-23 lack an inventive step under PCT Article 33(3) as being obvious over GROSENBACH et al. Synergy of vaccine strategies to amplify Antigen-specific Immune Responses and Anti-tumor Effects. Cancer Research. June 2001, vol. 61, 4497-4505 in view of US 6,537,552 B1 (MINION et al.) 25 March 2003 (25.3.2003).

GROSENBACH et al. provides guidance on a tumor vaccine therapy using an attenuated vaccinia (Wyeth) vector that encodes CEA and three co-stimulatory molecules (B7-1, ICAM-1, LFA-3) (Abstract; pg. 4498 Materials and Methods). Where the vaccine is co-administered with GM-CSF to enhance the T-cell responses and the vaccine/ GM-CSF combination is administered at three different time points over 28 days (pg. 4498 Materials and Methods).

MINION et al. supplements the guidance of GROSENBACH et al. by teaching a vaccine comprising a vaccinia virus encoding Muc-1 that is co-administered with GM-CSf, to treat pancreatic cancer (col. 6, line 55-col. 8, line 28; col.9, lines7-24)

Based on the guidance provided by GROSENBACH et al. it would have been obvious to the person of ordinary skill in the art at the time the invention was made to add the Muc-1 sequence taught by MINION et al. to the vaccinia vaccine taught by GROSENBACH et al. in order to produce a more vigorous T cell immune response against the pancreatic tumor.

The practitioner would be motivated to add the Muc-1 sequence taught by MINION et al. to the vaccinia vaccine taught by GROSENBACH et al. because GROSENBACH et al. teaches that a more vigorous T cell response produces a greater anti-tumor effect.

The person of ordinary skill in the art would have a reasonable expectation of success because the use of use of the Muc-1 sequence taught by MINION et al. comprises a minor modification to the vaccinia vaccine taught by GROSENBACH et al.

Claim 24 lacks an inventive step under PCT Article 33(3) as being obvious over the prior art as applied in the immediately preceding paragraph and further in view of US 5,827,666 (FINN et al.) 27 October 1998 (27.10.1998).

FINN et al. supplements the guidance of GROSENBACH et al. and MINION et al. by teaching how to make and use synthetic Muc-1-like analogs, consisting of tandem repeats of Muc-1 (Abstract). Where muc-1 like proteins containing multiple repeats that can be administered in order to inhibit the growth of pancreatic cancer (col. 5, lines 22-45; col. 6, lines 60-65). FINN et al. teaches that these proteins are superior at generating an immune response than MUC-1 since they contain repeated immuno-stimulatory epitopes (Col. 4, lines 40-67).

The practitioner would be motivated to use the tandem repeat Muc-1 sequence taught by FINN et al. in the vaccinia vaccine taught by GROSENBACH et al. because FINN et al. teaches that the multiple repeats are more immuno-stimulatory than the native MUC-1

The person of ordinary skill in the art would have a reasonable expectation of success because the use of the tandem repeat Muc-1 sequence taught by FINN et al. comprises a minor modification to the vaccinia vaccine taught by GROSENBACH et al.

Claims 1-24 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.